Unsuspected Pulmonary Emboli in Oncology Patients Undergoing Routine Computed Tomography Imaging

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Introduction: Clinically unsuspected pulmonary embolism (PE) can be detected in oncology patients undergoing computed tomography (CT) imaging for reasons other than for PE diagnosis, but there is little prospective data on its true prevalence, clinical importance, or on methods to improve detection.

Methods: In consecutive oncology patients undergoing CT imaging of the chest for indications other than PE detection, CT pulmonary angiography (CTPA) was systematically included as part of the imaging protocol. Each imaging study was prospectively analyzed for the presence of PE. A 6-month follow-up was performed. Institutional review board approval was obtained.

Results: Four hundred seven oncology patients were included. Indications for chest CT imaging included baseline staging (31%), restaging after therapy (53%), routine surveillance (15%), or assessment of extrathoracic disease (1%). Clinically unsuspected PE were detected in 18 patients (4.4%). The prevalence of unsuspected PE was 6.4% among inpatients and 3.4% among outpatients. PE was more prevalent among patients with metastatic disease (7% versus 2%, $p = 0.007$) and in patients who had received recent chemotherapy (11% versus 3%, $p = 0.008$). In 7 (39%) of the 18 patients with clinically unsuspected PE, emboli were only identifiable on the CTPA study and not on the routine chest CT study. The diagnosis of PE led to immediate changes in patient management.

Conclusion: Clinically unsuspected PE is present in up to 4.4% of oncology patients undergoing CT imaging for indications other than PE diagnosis. Modifying standard CT imaging protocols to include a CTPA examination optimizes their detection and leads to changes in patient management.

Key Words: Pulmonary embolism, Oncology, CT pulmonary angiogram, MDCT.

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Acute pulmonary embolism (PE) is a common and often fatal disease, occurring in approximately 600,000 patients annually in the United States and accounting for up to 150,000 deaths.[1] Most cases of PE that eventually cause fatality are clinically unsuspected and therefore go untreated before death.[2,3] Oncology patients have a fourfold higher risk for developing pulmonary embolism than that of the general population, increasing to sixfold if the patient is receiving chemotherapy.[4] In patients with cancer undergoing computed tomography (CT) imaging for reasons other than for PE detection, unsuspected PE has been found in up to 4% of overall cases and in up to 9% of inpatients.[5–7] Diagnosis of unsuspected PE is important to prevent embolic recurrence that is associated with substantial morbidity and mortality.[8]

CT pulmonary arteriography (CTPA) now represents the diagnostic test of choice for the diagnosis of PE and is widely available in most hospitals. The increasing availability of newer generations of multidetector CT scanners (16- and 64-slice) with rapid rotation speeds has made it possible to acquire thin-collimation images through large volumes of imaged tissue, allowing high-quality reconstructions using isometric voxels. In patients undergoing routine contrast-enhanced CT imaging of the thorax for indications other than PE detection, it is now possible to reconstruct the acquired data to provide thin-slice images of the pulmonary arteries equivalent to those in a CTPA study, provided that the contrast delivery has been timed to optimize opacification of the pulmonary arteries. By adjusting the imaging protocol accordingly, high-quality images of the pulmonary arteries can be acquired as part of a routine CT scan of the thorax. In oncology patients undergoing routine staging or restaging CT scans, we postulate that such an imaging protocol would improve detection of incidental PE, which may help to identify patients at risk for a subsequent major embolic event. The objective of our study was to evaluate the diagnostic usefulness of such a technique for the detection of clinically unsuspected PE in oncology patients and to determine its impact on patient management.

METHODS

This was a prospective longitudinal cohort study of consecutive oncology patients undergoing multidetector CT

imaging over a 10-month period from October 2007 to June 2008. The cohort comprised both inpatients and outpatients undergoing CT imaging of the thorax, abdomen, and pelvis for purposes other than PE detection. At our institution, we employ a standard CT protocol for staging and restaging of malignancies that comprises a contrast-enhanced CT of the thorax, abdomen, and pelvis. We enrolled only patients who would normally be imaged according to this protocol. Patients requiring different imaging protocols (e.g., dedicated liver, pancreas, or renal CT protocols) were excluded. Patient demographics (including age, sex, cancer diagnosis and stage, current or recent treatment, prior history of thromboembolic disease, indication for imaging, and the results of recent blood tests) were recorded for each patient from the patient's medical records. For the purposes of the study, tumor histology was categorized according to the general histologic classification used by the American Joint Committee on Cancer.[9] Cancer stage was broadly divided into those with localized (no metastatic or systemic disease) and those with evidence of systemic involvement (presence of metastases or stage IV disease). Patients were considered to have had recent chemotherapy if they had received treatment within the 30 days before their CT examination. Details regarding recent surgery and/or radiotherapy and current anticoagulation status were also recorded.

Exclusion criteria included patients with any pretest suspicion of pulmonary embolus; patients not undergoing complete CT scanning of the thorax, abdomen, and pelvis; patients with contraindications to IV contrast (allergy, renal insufficiency, and pregnancy); and patients in whom adequate IV access could not be obtained in the antecubital fossa. Patients requiring different imaging protocols (e.g., dedicated liver, pancreas, or renal CT protocols) were also excluded. Ethics approval was obtained from the local institutional review board.

Imaging Protocol

All scans were performed on a 64-slice multidetector CT scanner (Siemens 64 Somatom Emotion, Erlangen, Germany). The scanning protocol mandated a bolus intravenous injection of 100 to 150 mL iodinated contrast at 4 to 5 mL/sec via an antecubital vein along with a 20 mL saline flush; using a bolus-tracking technique (region of interest over the main pulmonary artery with a threshold of 100 Hounsfield units [HU]), the scan was triggered at the point of maximal pulmonary arterial enhancement (100 HU). A spiral CT scan of the thorax from the lung apices to the adrenal glands was acquired during this phase (kVp, 100–120; mAs adjusted according to weight with tube modulation; pitch, 0.9; rotation time, 0.5 seconds; collimation, 32 × 0.6 mm); delayed imaging of the abdomen and pelvis was subsequently performed during the phase of portal venous enhancement (40 seconds later). Images were reconstructed at 2 slice thicknesses: (a) for primary routine image interpretation, 5-mm axial slices were reformatted of the entire dataset; (b) in addition, for evaluation of the pulmonary arteries, contiguous thin (1 or 1.5 mm) slices of the thorax were systematically reformatted using soft tissue (window center, 40 HU; window width, 400 HU; B20f filter) and lung (window center, −600 HU, window width, +1600 HU; B80f filter) algorithms and window settings, respectively, providing an image subset of the pulmonary arteries equivalent to a diagnostic CTPA study. All images were archived electronically. We constructed into 5-mm slices as part of our routine protocol for all CT of the thorax, abdomen, and pelvis examinations. One millimeter slices of the thorax were performed for only those patients included in the study because of picture archiving and communication system (PACS) storage limitations.

Image Analysis

Each imaging study was prospectively evaluated on a dedicated PACS workstation by a radiology resident and an attending radiologist in consensus. Images (including both the routine CT and the CTPA components) were analyzed by scrolling through the dataset with the aid of a mouse; window settings were adjusted to provide optimal visualization of the pulmonary vasculature, which varied from patient to patient according to the degree of contrast enhancement.

For the purposes of the study, the overall diagnostic quality of the CTPA was evaluated based on the degree of opacification of the pulmonary arteries and the presence or absence of significant respiratory motion artifact. Studies that were considered nondiagnostic for the detection of PE were excluded from further analysis.

The presence and segmental location of incidental PE were recorded for each patient. The presence of PE on the CTPA images was defined according to established criteria (pulmonary arterial luminal filling defect on at least two consecutive axial images, associated with a crescent or ring of contrast enhancement surrounding partial filling defects).[10] Potential confounding artifacts were excluded (respiratory or cardiogenic motion artifact, crossing unopacified pulmonary veins, bronchial wall thickening, and peribronchial lymph nodes) by careful analysis of anatomy and adjacent lung parenchyma on both soft tissue and corresponding lung windows.[10,11]

Routine evaluation of CT of the thorax, abdomen, and pelvis with 5-mm slices was performed by the reporting consultant covering the list as per normal practice. Within 24 hours, review of the thin images (1 mm) was performed first by a radiology resident and then by a consultant radiologist on a dedicated PACS workstation. If a filling defect was identified on the thin slices, review of the thicker slice images was performed to evaluate whether the filling defect could have been diagnosed on the thicker slices and the same was recorded.

All scans prospectively considered positive for PE were reviewed and confirmed by two attending chest radiologists with at least 7 years of experience in interpreting multidetector CTPA examinations (J.B., J.M.). Detected pulmonary emboli were localized according to the modified Boyden classification of segmental pulmonary arterial anatomy.[12,13]

Follow-up of Patients with PE

In cases of a positive PE diagnosis, details were recorded regarding the presence or absence of any of the following: dyspnea, cough, hemoptysis, pleuritic chest pain, and leg swelling. Any prior history of diagnosis and treatment

of thromboembolic disease was documented. Details regarding the subsequent management of these patients were also recorded.

In addition, a later retrospective analysis was performed of all patients at least 6 months after their study protocol CTPA scan. This involved a review of all imaging studies performed on these patients over the 6-month period after their initial CTPA study (including repeat CT and CTPA examinations, venous doppler ultrasound studies, and ventilation-perfusion [V/Q] scintigraphic studies), to document the diagnosis of any new or recurrent venous thromboembolic events.

For all those patients with PE on CT, the 6-month follow-up included chart review and imaging review. All follow-up imaging was examined separately by a radiology resident and consultant radiologist along with the radiology report. All patients had at least 6 months follow-up. All patients had imaging in the subsequent 6-month period, and the exact timing of this was at the discretion of the referring clinician.

Statistical Analysis

Statistical analyses were performed using SPSS, version 15, software (SPSS, Chicago, IL). The prevalence of pulmonary emboli in each tumor group (according to histology) was compared with the prevalence in the entire study group by using the one-sided binomial test. The frequencies of abnormal laboratory values in the patients with and in those without pulmonary emboli were compared by using the χ^2 test. Logistic regression analysis was used to determine the statistical association between PE and patient age, patient sex, patient category (inpatient or outpatient), disease stage (metastases or no metastases), chemotherapy status (currently receiving or not), and cancer type (according to histology). A p value of 0.05 was considered to indicate a statistically significant difference.

TABLE 1. Patient Demographics of Total Study Group (n = 407)

Characteristics	*n* (%)
Male	179 (44)
Female	228 (56)
Age, yr (range)	60.7 (16–89)
Outpatient	267 (66)
Inpatient	140 (34)
Cancer types	
Breast cancer	124 (31)
Colorectal cancer	55 (14)
Lymphoma	53 (13)
Gynaecological cancer	31 (8)
Renal cell cancer	23 (6)
Lung cancer	22 (5)
Transitional cell carcinoma of bladder	19 (5)
Melanoma	18 (4)
Testicular cancer	10 (2.5)
Oesophageal cancer	9 (2)
Carcinoma of unknown primary	8 (2)
Squamous cell carcinoma	7 (1.5)
Pancreatic cancer	6 (1)
Others	22 (5)
General cancer stage	
Localized	218 (54)
Metastatic/stage IV	189 (46)
Chemotherapy	
Recent (within 30 d)	83 (20)
None/remote	316 (78)
Unknown	8 (2)
Indication for scan—no./total no. (%)	
Initial staging	127 (31)
Therapeutic response evaluation	215 (53)
Surveillance	59 (15)
Assessment of extrathoracic disease	7 (1)

RESULTS

A total of 408 patients were enrolled over a 10-month period. Of the 408 CTPA studies acquired, 99% were of either excellent (n = 397) or satisfactory (n = 10) image quality; one study was considered unsatisfactory, and this patient was excluded from further analysis. Three hundred ninety-six studies were reconstructed at 1-mm collimation and 11 studies were reconstructed at 1.5-mm collimation.

The remaining 407 study participants included 228 (56%) women and 179 (44%) men (mean age, 61 years; age range, 16–89 years), comprising 140 (34%) inpatients and 267 (66%) outpatients (Table 1). Indications for CT comprised initial baseline staging (31%), evaluation of therapeutic response after treatment (53%), routine surveillance while off treatment (15%), or assessment of extrathoracic disease (1%). Eighty-three (20%) patients had received chemotherapy within 1 month before their CT. Two hundred eighteen (54%) patients had localized disease at the time of scanning, whereas 189 (46%) had systemic or metastatic disease.

Incidental unsuspected PE was diagnosed in a total of 18 patients (4.4%) (Table 2). At the time of scanning, only one patient had dyspnea and cough, and one patient had chest pain; all the other patients had no clinical symptoms suggestive of PE. At the time of scanning patients, none of these patients were suspected to have PE by their referring clinicians.

The prevalence of unsuspected PE was 6.4% among inpatients and 3.4% among outpatients (p = 0.2). PE was seen most commonly in patients with colorectal carcinoma (5 of 18), followed by transitional cell carcinoma of the bladder, ovarian cancer, lymphoma, and esophageal cancer (2 of 18 each). The majority of patients with unsuspected PE had systemic or metastatic disease (14 of 18, 78%).

The prevalence of unsuspected PE was significantly higher among patients with metastatic malignancy (7%) than in patients with more localized disease (2%) (p = 0.007) and among patients who had received recent chemotherapy (11%) compared with patients who had not (3%) (p = 0.005). No other significant differences were seen between patients with and without PE. On logistic regression analysis, only recent chemotherapy was found to be a significant predictive factor for the likelihood of incidental PE (p = 0.008, 95% confidence interval 1.05–12.44).

TABLE 2. Patient Demographics of Patients with Unsuspected PE (n = 18)

Characteristic	n (%)
Male	9 (50)
Female	9 (50)
Age, yr (range)	61.6 (32–84)
Outpatient	9 (50)
Inpatient	9 (50)
Indication for scan	
Initial staging	5 (28)
Therapeutic response evaluation	10 (56)
Surveillance	2 (11)
Assessment of extra-thoracic disease	1 (5)
Cancer types	
Colorectal cancer	5 (28)
Lymphoma	2 (11)
Oesophageal cancer	2 (11)
Ovarian cancer	2 (11)
Transitional cell carcinoma of bladder	2 (11)
Breast cancer	1 (5.6)
Carcinoma of unknown primary	1 (5.6)
Melanoma	1 (5.6)
Pancreatic cancer	1 (5.6)
Renal cell carcinoma	
General cancer stage	
Localized	4 (22)
Metastatic/stage IV	14 (78)
Chemotherapy	
Recent (within 30 d)	9 (50)
None/remote	9 (50)
Coagulation status	
Normal	12 (66)
Mildly elevated INR	1 (6)
Mild thrombocytopenia	2 (11)
Mild thrombocytosis	3 (17)
Most proximal divisional location of PE per patient	
Main	4 (22)
Lobar	5 (28)
Segmental	6 (33)
Subsegmental	3 (17)

INR, international normalized ratio.

The most proximal arteries involved by PE comprised the main pulmonary artery (4 patients, 22%), a lobar pulmonary artery (5 patients, 28%), a segmental pulmonary artery (6 patients, 33%), or a subsegmental pulmonary artery (3 patients, 17%). In 15 (83%) patients, emboli were present in more than one pulmonary artery. Three (17%) patients had isolated subsegmental filling defects. Pulmonary emboli limited to the segmental or subsegmental pulmonary arteries were seen in 9 (50%) patients (Table 2, Figure 1).

In almost two-fifths (39%) of patients with PE, emboli were confidently visualized on only the thin 1-mm reformatted images and not on the thicker standard 5-mm slices. In the remaining 61% of patients, the emboli were easily visualized on both the thick and the thin slices.

Directed therapy with either systemic anticoagulation or an inferior vena cava filter was instituted in 17 of the 18 patients with incidental PE. One patient with an incidental isolated segmental PE was not treated with directed therapy because of coexistent thrombocytopenia and a presumed high risk of bleeding from anticoagulation therapy. This patient subsequently represented 5 weeks later with symptomatic multiple bilateral PE. There was no reported therapy related complications on chart or imaging review in the subsequent imaging period of those patients diagnosed with unsuspected PE.

At 6-month follow-up review of the patient cohort, there were no further thromboembolic events in the patients who had been diagnosed with PE at their initial CTPA and who had received anticoagulation. However, four other patients were diagnosed with clinically unsuspected PE on subsequent routine tumor monitoring CT examinations; in addition, six other patients presented with symptomatic PE, and two other patients presented with symptomatic deep vein thrombosis. None of these patients had evidence of pulmonary emboli on their initial protocol CTPA. In total, there were 22 (5.4%) oncology patients who were diagnosed with unsuspected PE at some point over a period of 6 months.

DISCUSSION

Our findings show that, by incorporating a CTPA study as a routine component of CT staging and restaging examinations in oncology patients, clinically unsuspected PE can be detected in up to 4.4% of patients, and that this changes patient management.

Oncology patients are known at be at an increased risk of venous thomboembolism that is up to four times that in the general population,[4,14] with a higher prevalence in inpatients and in those receiving chemotherapy. In addition to the hemostatic activation induced by the malignancy, oncology patients are exposed to a wide range of other factors that put them at increased risk for venous thromboembolic disease including central line placement, immobilization, and the thrombogenic effects of certain drugs.[14–16] Early detection of PE is important to reduce the morbidity and mortality associated with recurrent pulmonary emboli.[8]

Patients with cancer undergo frequent CT imaging of the chest for the purposes of diagnosis, staging, and surveillance and for evaluation of intercurrent illness related to the malignancy or its treatment. Previous studies have shown that incidental, clinically unsuspected PE can be detected on these CT examinations in 1.5 to 4% of patients[5–7,17,18] and in up to 9% of inpatients with malignancy.[5] Because of the high volume of oncology patients undergoing CT imaging on a routine basis, unsuspected PE is seen relatively frequently. However, most of these earlier studies have been based on analyses of CT scans performed on older generation technology, which have not been optimized for depiction of the pulmonary arterial vessels, and therefore, the true prevalence of unsuspected PE has remained uncertain.[7,19,20]

CT pulmonary angiography (CTPA) is currently the imaging modality of choice for the diagnosis of PE. It involves acquiring thin-slice CT images of the pulmonary

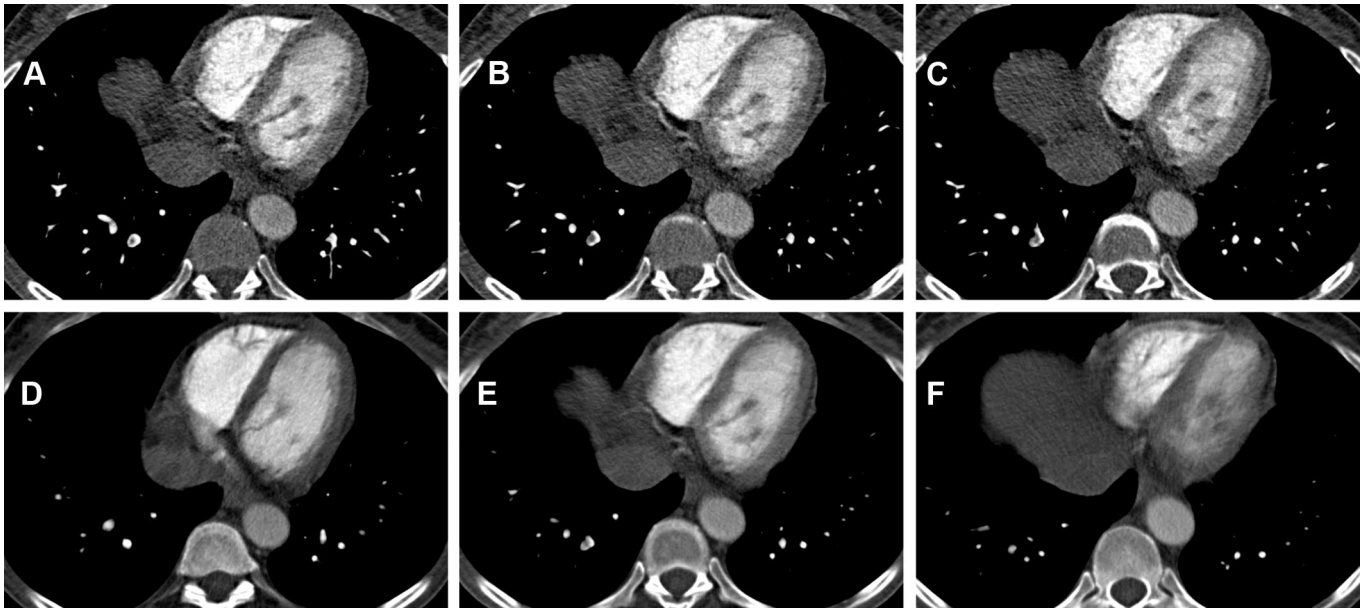

FIGURE 1. Radiographic images. *A–C*, Axial computed tomography (CT) images reconstructed at 1-mm thickness shows definite filling defects in two segmental pulmonary arteries in the right lower lobe pulmonary artery, which extended over consecutive axial images and met the diagnostic criteria for a diagnosis of pulmonary emboli (PE). *D–F*, Axial consecutive images of a routine restaging CT thorax at 5-mm thickness (same scan, same level, same window parameters as in *A–C* above) shows a subtle nonspecific filling defect in a segmental right lower lobe pulmonary artery, seen only on one slice (*B*), which did not meet diagnostic criteria for PE. The patient was completely asymptomatic at the time of scanning.

arteries during the phase of maximal pulmonary arterial contrast enhancement. The increasing availability of newer generation (16-slice and 64-slice) multidetector CT scanners has made it possible to acquire high-speed CT scans with thin collimation as a matter of routine. Using automated bolus tracking, fast acquisition speed, and thin collimation, modern multidetector scanners can achieve isometric volume acquisition that enables accurate depiction of peripheral subsegmental pulmonary arteries down to the level of sixth-order vessels.[21–23] Studies of CTPA have conclusively shown that the use of thinner slice thickness is associated with increased sensitivity for detection of PE in subsegmental vessels. Because up to 17% of patients with PE may only have isolated subsegmental emboli,[24] the use of thin-slice collimation is important for optimal PE detection. In contrast, in CT examinations performed for indications other than PE detection, image slice thicknesses of 5 to 10 mm are generally used, primarily for ease of interpretation and more efficient data storage.

As far as we are aware, ours is the first prospective study to systematically include an optimized CTPA protocol using thin-slice (1 and 1.5 mm) image reconstructions as an integral component of routine tumor monitoring CT scans in patients with cancer. This was achieved by ensuring that the delivery of IV contrast coincided with maximal pulmonary arterial enhancement by using an automated "bolus tracking" technique available on most multidetector CT scanners and by obtaining reformatted thin-slice (1 mm) axial images of the pulmonary arteries in all patients. It did not involve any additional radiation exposure to the patient. Using this technique, we found an incidence of clinically unsuspected PE in 4.4% patients (6.4% among inpatients and 3.4% among outpatients), which is consistent with that reported in other series.

Interestingly, in almost two-fifths (39%) of these patients, PE would not have been diagnosed without the thin-slice CTPA images. These patients had emboli limited to segmental and subsegmental vessels that, because of partial volume averaging effects, were partially obscured by high-attenuation contrast on thicker-slice images. Therefore, small segmental and subsegmental pulmonary emboli may be overlooked if pulmonary arterial analysis is limited to thick-slice images, even when the CT technique is optimized to obtain maximal pulmonary arterial contrast enhancement. The use of thin-slice reformats effectively eliminates partial volume averaging effect and improves diagnostic confidence.

Currently, there is no evidence to support the treatment of incidental PE. However, it still remains uncertain that not treating incidental PE is not associated with a risk of future events. It remains the responsibility of the interpreting radiologist to report if a PE is identified, and the onus is then of the clinician to determine optimal treatment on the clinician on whether or not to treat an unsuspected pulmonary embolus.[25] Small peripheral emboli, while not immediately life threatening, may cause pulmonary infarction resulting in pleuritic chest pain and hemoptysis; they may also herald larger and life-threatening emboli. Untreated recurrent PE can lead to chronic pulmonary thromboembolic disease and pulmonary arterial hypertension. In all but one of the patients in our study diagnosed with incidental PE, anticoagulation

therapy was instituted immediately, and these patients had no further thromboembolic events over the subsequent 6 months. The one patient who did not receive directed therapy had an isolated segmental PE; subsequently, 5 weeks later, he presented with multiple bilateral lobar and segmental pulmonary emboli, which were acutely symptomatic.

Modifying routine staging and surveillance CT protocols to include diagnostic quality CTPA examinations is easily achievable, but it poses logistical challenges in terms of data storage and image interpretation times. The acquisition of the additional CTPA study produces approximately an extra 200 images that need to be archived, effectively doubling the overall size of the entire CT study (220 MB versus 100 MB) and thereby increasing data storage costs. Interpretation of a CTPA study involves not only an analysis of the pulmonary arteries but also of the lung parenchyma for subtle abnormalities (such as small pulmonary nodules) that may have been missed on the routine thick-slice images, prolonging the reading time. This cost—both directly fiscal and indirectly fiscal in terms of image interpretation throughput—must be set against the gains in terms of improved PE detection and characterization of parenchymal abnormalities.

The results of the current and of prior studies emphasize the need to analyze the pulmonary arteries in all oncology patients undergoing CT imaging of the chest, particularly in inpatients, patients with advanced systemic or metastatic malignancy, and those having received recent chemotherapy. The detection of incidental PE will lead to significant changes in patient management; conversely, overlooking incidental PE may have adverse effects on patient outcomes. The current study describes a practical method for optimizing PE detection in oncology patients.

CONCLUSION

Our findings show that clinically unsuspected PE is present in up to 4.4% of oncology patients undergoing routine staging and surveillance CT scans. Modifying standard CT imaging protocols to include a CTPA examination optimizes their detection and leads to changes in patient management.

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